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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,054	11/17/2000	Gerald R. Crabtree	STAN-166	7611

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EXAMINER
COOK, LISA V

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/17/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,054	CRABTREE ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 16-39* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 25-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-3 and 16-39* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Amendment Entry

1. Applicant's response to the Office Action mailed 25 November 2002 is acknowledged. In amendment-C filed therein claim 16 was modified. Currently claims 16-24 are under consideration.

OBJECTIONS WITHDRAWN

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

The formal drawings filed 8/12/02 have been stamped approved by the draftsman under 37 CFR 1.84 or 1.152.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on form PTO-1449 have cited the references they have not been considered.

4. The information disclosure statement filed 2/10/03 - Paper#21 was considered as to the merits prior to Final Action.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 16-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 16 recites the limitation "an effective amount". The phrase remains indefinite because the claim fails to state the function which is to achieved. Although the claim recites the inhibition of a binding event, the detection of the inhibition has not been clearly defined. Accordingly the intended function is not clear/known. *In re Frederiksen,* 213 F2d 547, 102 USOQ 35 (CCPA 1954).

Applicant argues that the instant method is "therapeutic" in application, not requiring the detection of the inhibition. This argument was carefully considered but not found persuasive because the claims do not recite "therapeutic", but a method of inhibiting a binding event. It remains unclear as to how the method will inhibit a binding event without confirmation of binding inhibition via the detection of a determining factor (detection of the formed tripartite complex as a measure of inhibition). The method of claim 16 does not include a separation step or detection step wherein the complex formed in vivo will be identified to allow for correlation of binding inhibition.

B. Claim 16 remains vague and indefinite because it is unclear as to how binding inhibition will occur. Although the claim recites an interaction between a first target protein and a second binding protein in a host, the method does not clearly outline how the second protein and blocking protein interact such that inhibition of the first and second is accomplished. The claims merely read on the formation of a tripartic complex comprising the bifunctional inhibitor molecule, the target protein, and the blocking protein. But does not identify the correlation/interaction/detection allowing for comparative analysis between this tripartic complex and the second binding proteins inhibition. Will the blocking protein and second binding protein compete for the same binding site on the target protein therein allowing for measurement of the blocking protein as an inverse measure for the second binding protein. The method does not including essential method steps.

Applicant argues that the claims are not indefinite in light of the specification. The specification clarifies that the tripartite complex prevents access of the second protein to its binding site on the target protein. This argument was carefully considered but not found persuasive because although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F2d 1181, 26 USPQ 1057 (Fed. Cir. 1993).

6. Claims 16-24 remain rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are elucidated below:

Independent claims 16 is drawn to a method inhibiting a binding event between a first target protein and a second binding protein in a host. Merely reciting a method including the reagents, is not considered to be a proper method (including all the required method steps). Although the specification teaches methods on pages 20-21, the claims do not include the essential method steps. An assay or method, as proposed in the preamble of claims 1, require at least a contact step between reagents and sample, the separation of unbound and bound material, a detection step, and a correlation step. These essential steps for the method have not been outlined for determining protein-protein interaction inhibition. It is suggested that Applicant add steps that at least reflect: (I) a sample and reagent contacting step, (II) the binding or complex formation of a labeled product, the detection of the labeled product, and (III) a correlation step. Please include the necessary steps.

Applicant argues that the instant method is "therapeutic" in application, not requiring the detection of the inhibition. This argument was carefully considered but not found persuasive because the claims do not recite "therapeutic", but a method of inhibiting a binding event. It remains unclear as to how the method will inhibit a binding event without confirmation of binding inhibition via the detection of a determining factor (detection of the formed tripartite complex as a measure of inhibition). An assay method as proposed in claim 16, requires at least a contact step between reagents and sample, the separation of unbound and bound material, a detection step, and a correlation step. Claim 16 does not include a separation step or detection step wherein the complex formed in vivo will be identified to allow for correlation of binding inhibition.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 16-24 are rejected under #35 U.S.C. 102(b) as being anticipated by Griffith et al. (Cell, Vol.82, pages 507-522, August 11, 1995).

Griffith et al. disclose the ternary complex of calcineurin A fragment, calcineurin B, FKBP12, and the immunosuppressant drug FK506. The ternary complex provides a structural basis for understanding calcineurin inhibition by FKBP12-FK506. See abstract. The reference meets applicants claimed limitations by teaching the same reagents disclosed in the experimental design present on pages 20-21. The FKBP12-FK506 complex inhibits calcineurin phosphatase activity by blocking the active site from macromolecular phosphorylated substrates like NF-ATp. The information is further taught to be applicable as therapeutic inhibitors. Page 518, Conclusion.

Response to Argument

Applicant contends that the reference of Griffith et al. do not anticipate the instant invention because the distinct components are "not covalently bounded" to one another. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., covalent binding) are not recited in the rejected claim(s).

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further the linking group as defined on page 11 of the disclosure is optional.

With regard to the different method of producing the bifunctional molecules it is noted that the method of forming the product is not germane to the issue of patentability of the product itself. Therefore, this argument/limitation has not been given patentable weight.

Applicant argues that the FKBP12 protein has a molecular weight of at least 10,000 daltons, therein having a molecular weight of more than 5,000 daltons. However, this argument was not found persuasive because the disclosure lists various FKBPs further, citing FKBP12 as a blocking protein of particular interest. (page 9 line 22-23). Accordingly the limitation with respect to the weight of the molecule is inherent to the same recited molecule.

In response to the argument that Griffith et al. only discuss naturally occurring complexes, it is noted that various configurations are taught. Including non-naturally/modified constructs of retaining binding capacity. See page 515, 2nd column 1st paragraph.

Griffith et al. teach the instant invention in that it disclosed a complex formed from FK506-FKBP12-Calcineurin. Wherein bound FKBP12 physically blocks access by NF-Atp. See page 515, 2nd column – Inhibition of Cal....

II. Claims 16-21 and 24 are rejected under #35 U.S.C. 102(b) as being anticipated by Varshavsky (Proc. Natl. Acad. Sci. USA Vol.95, pp. 2094-2099, March 1998).

Varshavsky teaches multitarget compounds specific for negative targets concerning the concept of codominant interference. The reference discloses compositions linking two small moiety ligands (< 1Kd page 2095) bipartite compounds consisting of two ligands bound together by a linker (1* and c in Fig. C and D). The ligands are capable of simultaneously binding target protein (C in figure D) and blocking proteins (1 in figure C) thereby possibly forming a tripartite complex. Multitarget drugs designed according to the specific configurations taught by Varshavsky were taught to be useful in the selective killing of cancer cells via the inhibition of a neurotransmitter-inactivating enzyme in a specific subset of the enzyme-containing cells. Therein teaching protein-protein inhibition. See abstract.

Response to Argument

In response to the argument that abi is not a tripartite complex as produced in the claimed methods, it is noted that the method of producing the compounds are not under consideration. Drug interaction to exhibit the formation of a tripartite complex is disclosed by Varshavsky. Accordingly a tripartite complex (consisting of at least three components a-b-I further linked to A, B, or I teaches the instantly claimed invention.

Applicant contends that Varshavsky et al. teach or suggest binary complexes of either a bifunctional molecule and its target or a bifunctional molecule and a second protein that prevents the bifunctional molecule from binding to the target. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., non-covalent binding) are not recited in the rejected claim(s).

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further the linking group as defined on page 11 of the disclosure is optional.

With regard to the different method of producing the bifunctional molecules it is noted that the method of forming the product is not germane to the issue of patentability of the product itself. Therefore, this argument/limitation has not been given patentable weight.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Varshavsky (Proc. Natl. Acad. Sci. USA Vol.95, pp. 2094-2099, March 1998)in view of Pouletty et al. (WO 95/10302).

Please see previous discussions of Varshavsky as set forth above.

Varshavsky differ from the instant invention in failing to teach tripartite complexes produced extracellularly.

However, Pouletty et al. teach bifunctional reagents useful in extending in vivo lifetimes of physiologically active agents further reducing the biologically effective concentration or activity of an endogenous or exogenous blood component. Page 2, lines 14-20. A target binding member, which is a physiologically active agent in a mammalian host is bound to a protein via a reagent or conjugate possibly including a linking group. See pages 19 and 20. Applicable proteins include albumin, transferrin, ferritin, and immunoglobulins. See page 3, lines 5-25. The second binding member is usually a macromolecule of at least 5000 Dalton. Page 25, lines 20-25. The bifunctional reagents are taught to have utility in therapeutic methods to detect host derived and foreign targets. Page 5, lines 6-10.

Varshavsky and Poulett et al. are analogous art because they are from the same field of endeavor, both inventions teach techniques involving bifunctional reagents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the proteins endogenous to the host (i.e. albumin, vitamin receptor, etc..) as taught by Poulett et al. in the method of Varshavsky to perform protein-protein inhibition assay techniques, because such endogenous proteins as taught by Poulett et al. are well known in the art.

A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such endogenous proteins, because Poulett et al. taught that the selected blocking protein (long-lived blood component) would affect the manner in which the biological activity of the target is modified and the selection will vary dependent on the nature of the target.

Page 30, lines 23-30. In other words compounds endogenous to the host would cause less side effects and extend dosage levels. Page 1, lines 26-30.

One having ordinary skill in the art would have been motivated to do this because the blocking protein can impart its physiological activities to the target binding member. In this way cellular targets may be inactivated or eliminated. Page 33, lines 16-22.

Response to Argument

Applicant contends that the Varshavsky teaches away from the claimed because the reference only teaches binary complexes. However Varshavsky teaches complexes binding at least four components (a, b, i, along with A,B, or I).

9. For reasons aforementioned, no claims are allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Remarks

11. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Weiderrecht et al. (U.S. Patent#5,457,182) teach binding interactions involving FK-506 and FKBP12.6.

B. Maragarnore et al. (U.S.Patent#5,242,810) disclose bifunctional inhibitors of platelet activation and thrombin.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
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6/18/01

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